

DGMC – Human Research  
Final Report

**1. DATE: 10 April 2014**

**2. Protocol Number: FDG20010007H RTOG9902**

**3. Title:** A Phase III Protocol of Total Androgen Suppression (TAS) and Radiation Therapy (RT) vs TAS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) for Localized, High-Risk, Prostate Cancer

**4. Risk:** ☒ Greater than Minimal Risk      ☐ Minimal Risk

**5. Date of Approval:** 6 Nov 2000

**6. Start Date:** 17 Nov 2000

**7. Study Staff**

| Name                 | Rank   | Study Role | Date of Investigator Training | Staff/ Resident/ Fellow/ Civilian | Dept/ Office Symbol | Phone    | E-mail                          |
|----------------------|--------|------------|-------------------------------|-----------------------------------|---------------------|----------|---------------------------------|
| Mitchell, James      | Maj    | PI         | 11/26/12                      | Staff                             | SGQXO               | 423-7691 | James.mitchell.6@us.af.mil      |
| David Eastham        | Lt Col | AI         | 2/10/13                       | Staff                             | SGQXO               | 423-7691 | David.eastham@us.af.mil         |
| David J Hoopes       | Maj    | AI         | 8 April 2011                  | Staff                             | SGQXO               | 423-3673 | <u>David.Hoopes.1@us.af.mil</u> |
| Natalia I Knezienski | Civ    | CRC        | 4 April 2012                  | Civ                               | SGQXO               | 423-7691 | Natalia.Knezienski.1@us.af.mil  |

**8. Study Status:**

(Check one only)

- ☐ Inactive, protocol never initiated  
☐ Inactive, protocol initiated but has not/will not be completed  
☒ All approved procedures/uses have been completed

**9. Number of Subjects Entered into the Study:** For multiple sites, add rows to the table below for each site.

|  | Number approved to enroll | Number enrolled | Withdrawals       |
|--|---------------------------|-----------------|-------------------|
| Number of subjects enrolled at DGMC                            | not determined            | 2               | 0                 |
| Number of subjects enrolled at National RTOG Cooperative Sites | 1440                      | 397             | 17 (not eligible) |

| Report Documentation Page  |                                | Form Approved<br>OMB No. 0704-0188                   |
|--|--------------------------------|--|
| Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. |                                |  |
| 1. REPORT DATE<br><b>13 MAY 2014</b>   | 2. REPORT TYPE<br><b>Final</b> | 3. DATES COVERED<br><b>06 NOV 2000 - 13 MAY 2014</b> |
| 4. TITLE AND SUBTITLE<br><b>FDG20010007H, RTOG #99-02 A Phase III protocol of androgen suppression and radiation therapy Vs and RT followed by chemotherapy with paclitaxel, estramustine, and etoposide for localized, high risk, prostate cancer.</b>  |                                | 5a. CONTRACT NUMBER                                  |
|  |                                | 5b. GRANT NUMBER                                     |
|  |                                | 5c. PROGRAM ELEMENT NUMBER                           |
| 6. AUTHOR(S)<br><b>Lt Col Davis Eastham, Maj James Mitchell, Maj David Hoopes, Maj Hristov Borislav, Lt Col Ronald Engel</b>   |                                | 5d. PROJECT NUMBER<br><b>FDG20010007H</b>            |
|  |                                | 5e. TASK NUMBER                                      |
|  |                                | 5f. WORK UNIT NUMBER                                 |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br><b>Clinical Investigation Facility David Grant Medical Center 101 Bodin Circle Travis AFB, CA 94535</b>  |                                | 8. PERFORMING ORGANIZATION REPORT NUMBER             |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)<br><b>Clinical Investigation Facility David Grant Medical Center 101 Bodin Circle Travis AFB, CA 94535</b>   |                                | 10. SPONSOR/MONITOR'S ACRONYM(S)                     |
|  |                                | 11. SPONSOR/MONITOR'S REPORT NUMBER(S)               |
| 12. DISTRIBUTION/AVAILABILITY STATEMENT<br><b>Approved for public release, distribution unlimited</b>  |                                |  |
| 13. SUPPLEMENTARY NOTES  |                                |  |

## 14. ABSTRACT

**Summary of Protocol Objectives:** The primary objectives were to assess the relative efficacy of the combination of androgen suppression (AS) plus radiation therapy (RT) followed AS vs. AS plus RT followed by chemotherapy (CT) plus AS in high risk, unfavorable prognosis prostate cancer (PCa) population. In order to measure the efficacy of the treatments the endpoints being evaluated were overall survival, disease free survival, local control and freedom from distant metastasis. Differences in toxicities between the two treatments were also going to be evaluated. The RTOG 9902 investigators hypothesize that adjuvant CT would improve the survival rate of high-risk PCa when used in combination with RT and AS. **Methods:** The purpose and methods were reviewed and approved by the local IRB. The voluntary and full informed consent of participants was obtained prior to study procedures. Volunteer participants who met eligibility criteria were stratified, enrolled and randomized as per protocol. In brief, eligibility criteria included men with high risk non metastatic prostate cancer histologically confirmed with PSA level of 20-100ng/mL and a Gleason score > 7, stage T2 or greater. Volunteer participants were randomized into one of two treatments. RT began 8 weeks after androgen suppression treatment and followed weekly by their radiation oncologist during the RT, every 3 months for two years, then every 6 months for three years and yearly after that for the remainder of the participants natural life. **Results:** Study was locally approved on November 2000 and assigned number FDG20010007H, receiving 10 continuing approval before IRB oversight was transferred to Wilford Hall (WHMC) under protocol number FWH20110083H. IRB oversight was transferred back DGMC in May 2012. This study opened nationally in Jan 2000 and prematurely closed to accrual in Oct 2004 with a total of 397 participants (380 eligible); 2 from DGMC. The protocol has been deemed terminated by national RTOG-9902. We have one participant still enrolled in the study from which data collection will cease and monitoring will continue as standard of care throughout the remainder of his natural life as per latest RTOG broadcast (Nov2013). RTOG 9902 investigators previously reported on the chemotherapy combination toxicities that led to early protocol closure (Rosenthal, et al. IJROBP 73:672, 2009), also reported with local yearly reviews (2005, 2012). Nevertheless, participants have been followed for the primary endpoint. Overall study compliance was 98-99% for Arm-1 and Arm-2, respectively. Median follow-up was 6 years; 5-yr overall survival was 86% for both the RT+AS and RT+AS+CT arms (p=0.79). **Conclusions:** RTOG 9902 failed to reach its accrual goal due to toxicity. Investigators found no difference in overall survival with the addition of adjuvant CT. Of note, small sample size due to premature closure may have reduced the ability to detect a significant difference. However the study revealed that patients are willing to be randomized into chemotherapy and that chemotherapy as an adjuvant does not present significant late gastro and genitourinary toxicities and it is being evaluated. A similarly designed trial, RTOG 0521, completed accrual in 2009, will shed light into adjuvant chemotherapy with a different combination (rather than TEE).

## 15. SUBJECT TERMS

## 16. SECURITY CLASSIFICATION OF:

a. REPORT

**unclassified**

b. ABSTRACT

**unclassified**

c. THIS PAGE

**unclassified**17. LIMITATION OF  
ABSTRACT**SAR**18. NUMBER  
OF PAGES**7**19a. NAME OF  
RESPONSIBLE PERSON

### 9.1. Summary of Unanticipated Problems and Adverse Events:

The study had *Local* Unanticipated Problems:

☐ Yes ☒ No

The study had *Local* Adverse Events:

☒ Yes ☐ No

All *Local* adverse, serious adverse and unexpected events were reported IAW SGSE 40-402-01:

☒ Yes ☐ No ☐ N/A

List all the local and sponsor reported unanticipated problems, serious and non-serious adverse events, reported to the sponsor and protocol deviations that resulted in subject harm for the entire study. **If none occurred, state NONE.**

FDG20010007H/RTOG-9902 ran active enrollment for a total of 4 years. Study was prematurely halted due to higher than anticipated SAE on one of the randomization arms (Arm-2) of the trial. At DGMC we had two participants (as of 2004) one of which was enrolled in Arm-2. As per RTOG direction participant was re-assigned to Arm-1 with a treatment change (2005 CR report). RTOG 9902 study also reported 2 deaths in Arm-2 (due to sepsis). At DGMC we reported one death in 2004. There were no reported protocol deviations at DGMC that resulted in subject harm.

| Type of Event* | Date of Event | Date Reported        | Description of Event                           | Site of Event (for multisite) | Outcome  |
|----------------|---------------|----------------------|--|-------------------------------|--|
| SAE            | 17 APR 02     | 23 APR 02<br>by RTOG | Increased thromboembolic and other toxicities  | RTOG-Nat                      | DSMB-temporary halt study APR02-JUN02. Protocol amendment to address anticoagulation regimen |
| SAE            | 30 JUL 04     | 4 OCT 04<br>by RTOG  | Persistent thromboembolic and other toxicities | RTOG-Nat                      | DSMB-premature closure. Continue follow up of enrolled                                       |
| SAE            | 4 FEB 04      | 24 JUN 04            | Participant expiration                         | DGMC                          | Report/Notification of death   |
|                |               |                      |  |                               |  |

\*Unexpected adverse event, severe adverse event, or adverse event

Reminder if these events were study related, caused harm or increased the risks to subjects or others, they should have already been reported when discovered, using the Adverse or Unexpected Adverse Event report form. This is only a summary of those events.

**9.2. Summary of Withdrawals from the Study: If none occurred, state NONE.** List all subjects who withdrew (please specify if the subject withdrew, is lost to follow-up, deceased or any other reasons from your study)

#### For the Entire Study Chronologically

| Date of Withdrawal | Subject Number | Reason for Withdrawal |
|--------------------|----------------|-----------------------|
| none               |                |                       |

### 9.3. Consent Process:

Each participant was recruited in accordance with the recruitment plan approved by the IRB.

☒ Yes ☐ No

Each participant was consented in accordance with the consent process approved by the IRB.

☒ Yes ☐ No

Each participant was given a copy of the signed, dated informed consent document.

☒ Yes ☐ No

As the PI, I have retained a copy of each participant's signed, dated informed consent document and provided a copy to the Protocol Office for record.

☒ Yes ☐ No

### 10. Study Deviations

Have any minor non-compliance events occurred?

☒ Yes ☐ No

Have any serious non-compliance events occurred?

☐ Yes ☒ No

List any instances of non-compliance minor or serious

Local minor non-compliance activities were noted during an audit conducted on 1MAR2010. Protocol deviation was reported for a consent form misplaced on 02APR2009. These activities did not cause harm or affect the rights and/or welfare of study participants and have been reported appropriately to the respective regulatory bodies. Furthermore, corrective/preventive actions were put in place to prevent reoccurrence.

I certify that no changes have occurred in the protocol since the previous IRB review.

☒ Yes ☐ No

### 11. Complaints about the Study:

Have there been any reported complaints regarding the study?

☐ Yes ☒ No

List all complaints about your study, for the Entire study. If no complaints occurred, state **NONE** and delete the table below. Do not use N/A

**NONE**

### 12. Amendments:

List all amendments/changes made to the protocol, Informed Consent or investigator's brochure. **IF none occurred, state NONE. Do not use N/A.**

| Date of Change | Date of Approval | Summary of the Change   |
|----------------|------------------|---|
| 18-Oct-01      | 18-Oct-01        | <b>DGMC Amendment 1:</b> Change of PI from Col William Dickerson to Maj Roland Engel. Addition of Col William Dickerson as AI |
| 1-Aug-02       | 1-Aug-02         | <b>DGMC Amendment 2:</b> Deletion of Col William Dickerson due to military transfer   |
| 31 Jul 03      | 4-Aug-03         | <b>DGMC Amendment 3:</b> RTOG National Amendments #1, #2 and #3: Changes in protocol content and ICD                          |
| 18 Apr 04      | 16 Apr 04        | <b>DGMC Amendment 4:</b> RTOG National Amendment# 4: Changes in protocol content and ICD                                      |
| 5 Apr 04       | 21 Apr 04        | <b>DGMC Amendment 5:</b> Addition of Dr. Belinda Ark and Capt   |

|           |           |  |
|-----------|-----------|--|
|           |           | Carolyn A. Wild as AIs   |
| 2 Sep 09  | 4 Oct 09  | <b>DGMC Amendment 6:</b> Adding two AIs: Maj Vincent Lee and Capt Borislav Hristov, and<br>RTOG National Amendment#5: Changes in protocol content    |
| 23-Jul-10 | 2 Aug 10  | <b>DGMC Amendment 7:</b> Deletion of Maj Vincent Lee due to separation from the AF   |
| 12-Oct-10 | 1-Nov-10  | <b>DGMC Amendment 8:</b> Personnel Change in PI from Col Engel (PCS) to Maj David Hoopes   |
| 18 Apr 13 | 26 Apr 13 | <b>DGMC Amendment 9:</b> Change of PI from Maj Hoopes to Maj James Mitchell; Maj Hoopes will remain as AI. Also to add Lt Col David Eastham as an AI |

### 13. Funding:

(Complete as appropriate, delete the others, some of this information is contained in your protocol and or amendments – suggest you cut and paste info. As a reminder, requests for additional funding must be submitted using the Protocol Amendment form.

Funding from:

☐ R&D ☐ SGO ☐ O&M ☐ HMJ ☒ OTHER (explain source): RTOG/JROC

in the amount of \$ N/A was approved in my original protocol. Of that money, I will need \$ N/A for the remainder of this fiscal year.

I have received External Resources to support this study in the form of:

(select all those applicable):

- ☐ Loaned equipment  
☐ Consumable supplies  
☐ Drugs from a non-DoD source

### 14. Summary of Research Findings:

**Summary of Protocol Objectives:** The primary objectives were to assess the relative efficacy of the combination of androgen suppression (AS) plus radiation therapy (RT) followed AS vs. AS plus RT followed by chemotherapy (CT) plus AS in high risk, unfavorable prognosis prostate cancer (PCa) population. In order to measure the efficacy of the treatments the endpoints being evaluated were overall survival, disease free survival, local control and freedom from distant metastasis. Differences in toxicities between the two treatments were also going to be evaluated. The RTOG 9902 investigators hypothesize that adjuvant CT would improve the survival rate of high-risk PCa when used in combination with RT and AS.

**Methods:** The purpose and methods were reviewed and approved by the local IRB. The voluntary and full informed consent of participants was obtained prior to study procedures. Volunteer participants who met eligibility criteria were stratified, enrolled and randomized as per protocol. In brief, eligibility criteria included men with high risk non metastatic prostate cancer histologically confirmed with PSA level of 20-100ng/mL and a Gleason score > 7, stage T2 or greater. Volunteer participants were randomized into one of two treatments. RT began 8 weeks after androgen suppression treatment and

followed weekly by their radiation oncologist during the RT, every 3 months for two years, then every 6 months for three years and yearly after that for the remainder of the participant's natural life.

Results: Study was locally approved on November 2000 and assigned number FDG20010007H, receiving 10 continuing approval before IRB oversight was transferred to Wilford Hall (WHMC) under protocol number FWH20110083H. IRB oversight was transferred back DGMC in May 2012. This study opened nationally in Jan 2000 and prematurely closed to accrual in Oct 2004 with a total of 397 participants (380 eligible); 2 from DGMC. The protocol has been deemed terminated by national RTOG-9902. We have one participant still enrolled in the study from which data collection will cease and monitoring will continue as standard of care throughout the remainder of his natural life as per latest RTOG broadcast (Nov2013). RTOG 9902 investigators previously reported on the chemotherapy combination toxicities that led to early protocol closure (Rosenthal, et al. IJROBP 73:672, 2009), also reported with local yearly reviews (2005, 2012). Nevertheless, participants have been followed for the primary endpoint. Overall study compliance was 98-99% for Arm-1 and Arm-2, respectively. Median follow-up was 6 years; 5-yr overall survival was 86% for both the RT+AS and RT+AS+CT arms ( $p=0.79$ ).

Conclusions: RTOG 9902 failed to reach its accrual goal due to toxicity. Investigators found no difference in overall survival with the addition of adjuvant CT. Of note, small sample size due to premature closure may have reduced the ability to detect a significant difference. However the study revealed that patients are willing to be randomized into chemotherapy and that chemotherapy as an adjuvant does not present significant late gastro and genitourinary toxicities and it is being evaluated. A similarly designed trial, RTOG 0521, completed accrual in 2009, will shed light into adjuvant chemotherapy with a different combination (rather than TEE).

#### 15. Publications and Presentations for this research study:

List all presentations **Authored by study staff** (Include lectures, abstracts, posters, etc), for the Entire study. **For RTOG and other national collaborations please include publications and presentations directly tied to the approved protocol only.**

| Date   | Authors   | Title  |
|--|---|--|
| 1 Nov 2012   | Hamstra D.A., Hunt D., Grignon D., Hanks G.E., Peters C.A., Rosenthal S.A., Lock M.I., Zeitzer K.L., Souhami L., and Sandler H. | Gleason Pattern 5 is Associated With an Increased Risk for Metastasis Following Androgen Deprivation Therapy (ADT) and Radiation: An Analysis of RTOG 9202 and 9902<br><i>Int J Radiat Oncol Biol Phys.</i> 2012 doi:10.1016/j.ijrobp.2012.07.240<br><i>Oral Scientific Session 225</i>  |
| 4-8 June 2010<br>Proc of American Society of Clinical Oncology (ASCO) Annual Meeting | Sandler H, Hunt D, Sartor A, Gomella L, Hartford A, Zeitzer K, Rajan R, Kerlin K, Michalski J, Rosenthal S.                     | A Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) versus AS and RT Followed by Chemotherapy with Paclitaxelkestramustine, and Etoposide (TEE) for Localized, High-Risk, Prostate Cancer<br>Poster Presentation  |
| 1 March 2009   | Rosenthal S, Bae K, Pienta K, Hartford A, Asbell S, Rajan R, Kerlin K, Michalski J, Sandler H.                                  | Phase III Multi-Institutional Trial of Adjuvant Chemotherapy (CT) with Paclitaxel, Estramustine, and Oral Etoposide in Combination with Long-Term Androgen Suppression (AS) Therapy and Radiation Therapy (RT) vs. Long-Term AS + RT Alone in the Management of High-Risk Prostate Cancer: Preliminary Toxicity Analysis of RTOG 99-02. <i>Int J Radiat Oncol Biol Phys.</i> 2009; 73 (3): 672-678.<br><a href="http://www.ncbi.nlm.nih.gov/pubmed/18990504">http://www.ncbi.nlm.nih.gov/pubmed/18990504</a><br><i>Journal Article</i> |

Protocol Title: Phase III protocol of TAS and RT vs.  
TAS and RT followed by chemotherapy with TEE for  
localized high-risk prostate cancer  
FDG#20010007H RTOG-9902

Maj Mitchell, J.

DGMC Human Final Report Template

These presentations/publications were approved by the CIF Director and Public Affairs Office.

☐ Yes ☐ No **NON applicable**, non-local publications



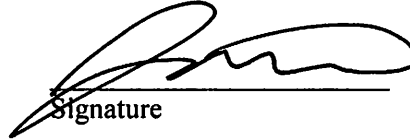
Protocol Title: Phase III protocol of TAS and RT vs.  
TAS and RT followed by chemotherapy with TEE for  
localized high-risk prostate cancer  
FDG#20010007H RTOG-9902

Maj Mitchell, J.

DGMC Human Final Report Template

**16. Signature of Principal/Associate Investigator:**

James D. Mitchell, MD  
Type/Print Name of Investigator

  
Signature

4/18/14  
Date

CC: Research Monitor (RM) Name  
(Forward a copy of this report to RM.)

**Attachments:**

Please list attachments below and attach to Progress Report  
e.g. amendments, publications